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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,264	03/31/2004	Narayanan Sundararajan	21058/0206768-US0	7476

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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1797	

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01/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,264	SUNDARARAJAN ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-14,16-20 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14,16-20 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 24, 2007 has been entered.

2. Claims 10-12 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In paragraph [0013], optical tweezers are defined as "typically a gradient force optical trap". Thus with the addition of the new language it is not clear if there are now two tweezers required by the claim or if the added "operable as an optical tweezers" language was not necessary. For examination purposes, the latter will be treated as the scope of the claims based on the above definition of the instant specification. In claim 18, "the gradient force optical trap does not have antecedent basis.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 10 and 46 are rejected under 35 U.S.C. 102(a,b) as being anticipated by Dorre or Namba (JP-2003-189852).

In the paper Dorre teaches techniques for single molecule sequencing. A method is described that demonstrates a new technique for rapid and high-throughput single molecule sequencing. This sequencing technique is based on the successive enzymic degradation of fluorescently labeled single DNA molecules, and the detection and identification of the released monomer molecules according to their sequential order in a microstructured channel. The detection technique is evolved from confocal fluorescence microscopy, with two different laser sources to excite the individual mononucleotides that are either labeled with tetramethylrhodamine (TMR) or Cyanine5 (Cy5). The handling of DNA which is immobilized on carrier beads, and the detection of the cleaved monomers is performed in optically transparent

and biochemically inert microstructures (glass or PMMA) with detection channels of 7 μm × 10 μm. The projected rate of sequencing is ≈ 100 bases per minute, dependent solely on the rate of the enzymic DNA cleavage. The structure of the apparatus is shown in figures 1 and 4. Figure 4a shows junctions of several channels with the first channel. The microstructured channel has a restriction barrier (narrowing of the channel) consisting of first and second angled walls. The paragraph bridging pages 142-143 teaches the above 7 μm × 10 μm dimensions for the narrowest part of the channel with even smaller dimensions 6 μm × 7 μm as having been used. Thus the dimensions for the widths of the first and second openings are within the ranges of claim 10. Figure 1 clearly shows that there is a trap laser. The paragraph bridging the columns of page 140 teaches that this IR trap laser focus is an 'optical tweezers'.

In the published application, Namba teaches confocal fluorescence microscopy for single molecule DNA sequencing. A method and apparatus are described that demonstrates a new technique for rapid and high-throughput single molecule DNA sequencing. This sequencing technique is based on the successive enzymic degradation of fluorescently labeled single nucleic acid molecules, and the detection and identification of the released mononucleotides according to their sequential order in a microstructured channel. The detection technique is evolved from confocal fluorescence microscopy, with two different laser sources to catch DNA containing particles for enzymic degradation and excite the individual mononucleotides that are labeled with fluorescent material. The handling of DNA which is immobilized on carrier beads, and the detection of the cleaved monomers is performed in optically transparent and biochemically inert microstructures (glass or PMMA) with detection channels of 7 μm × 10 μm. The apparatus also comprises an optical detector. Figure 4 shows an example of a measuring cell with a restriction barrier using first and second angled walls to narrow the channel width. Paragraph [0050] teaches dimensions for the width of the narrow part of preferably between 5 and 50 micrometers (see translation) which clearly includes dimensions within the instantly claimed range. Figures 6 and 7 show embodiments in which a trap laser and an excitation laser are clearly labeled.

Paragraphs [0105] to [0109] discuss the capture or catching laser and refer to the use of optical tweezers for such a purpose (see translation).

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 12-14, 16-17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorre or Namba as applied to claims 10 or 46 above, and further in view of Ishikawa or Kneipp (US 2002/0150938, Physical Review E 1998, or Indian Journal of Physics, B abstract in chemical abstracts, hereinafter referred to as Kneipp 2002, Kneipp '98 and Kneipp '03, respectively). Dorre and Namba do not teach surface enhanced Raman Spectroscopy as a detector or a junction with a channel downstream or the restriction barrier.

In the paper Ishikawa teaches single-molecule imaging and spectroscopy using fluorescence and surface-enhanced Raman scattering. They extended single molecule fluorescence imaging and time-resolved fluorometry from the green to the violet-excitation regime to find feasibility of detecting and identifying fluorescent analogs of nucleic-acid bases at the single-molecule level. Using violet excitation, they observed fluorescent spots from single complexes composed of a nucleotide analog and the Klenow fragment of DNA polymerase I. Also, they implemented Raman imaging and spectroscopy of adenine molecules adsorbed on Ag colloidal nanoparticles to find feasibility of identifying nucleic-acid bases at the single-molecule level. Surface enhanced Raman scattering (SERS) of adenine molecules showed an intermittent

on-and-off behavior called blinking. The observation of blinking provides substantial evidence for detecting single adenine molecules.

In the published application Kneipp 2002 teaches single molecule detection with surface-enhanced Raman scattering and applications in DNA or RNA sequencing. Surface-enhanced spectroscopy, such as surface-enhanced Raman spectroscopy employs aggregates that are of a size that allows easy handling. The aggregates are generally at least ~500 nm in dimension. The aggregates can be made of metal particles of size <100 nm, allowing enhanced spectroscopic techniques that operate at high sensitivity. This allows the use of larger, easily-handleable aggregates. Signals are determined that are caused by single analytes adsorbed to single aggregates, or single analytes adsorbed on a surface. The single analytes can be DNA of RNA fragments comprising at least one base.

In the paper Kneipp '98 teaches detection and identification of a single DNA base molecule using surface-enhanced Raman scattering (SERS). Nonresonant Raman cross sections of $\sim 10^{-16}$ cm^2 per molecule are shown to be related to surface-enhanced Raman scattering (SERS) on colloidal silver clusters at near-IR (NIR) excitation. The enhancement is independent of cluster sizes between 100 nm and 20 μm. These experimental findings demonstrate that NIR SERS on colloidal silver clusters is an excellent technique for single molecule detection that is applicable for a broad range of molecules including "colorless" biomolecules, for example nucleotides in DNA sequencing. As an example, a single adenine molecule without any labeling is detected based on its intrinsic surface-enhanced Raman scattering.

In the abstract of the paper Kneipp '03 teaches single molecule Raman spectroscopy using silver and gold nanoparticles. The authors discuss single molecule Raman spectroscopy based on the strongly enhanced Raman scattering signals which occur when a target molecule is attached to Ag and Au colloidal nanoparticles. This phenomena known as surface-enhanced Raman scattering (SERS) exploits extremely large SERS enhancement factors of about fourteen orders of magnitude, with effective Raman cross sections reaching the level of fluorescence cross sections thus enabling a single molecule detection using surface-enhanced Raman spectrum. The advantage of this method is that it not only detects a single molecule, it also simultaneously provides its structural fingerprint. Also, SERS can be studied under electronic nonresonant

conditions, which avoids photobleaching. Detecting single molecules as well as identifying their chemical structures represents the ultimate limit in chemical analysis and is of great practical interest in many fields. This paper gives a brief introduction to single molecule SERS spectroscopy, describes nonresonant single molecule Raman experiments at near IR excitation and discusses prospects and limitations of the method.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to relapse the fluorescence detector of Dorre or Namba with the surface enhanced Raman scattering detectors of Ishikawa, Kneipp 2002, Kneipp '98 or Kneipp '03 because of the ability to detect nucleotides at the single molecule level as shown by each of Ishikawa, Kneipp 2002, Kneipp '98 and Kneipp '03 and the advantages such as no requirement to add a label (colorless molecules) of Kneipp '98 or the structural identification of the molecule in addition to its detection as taught by Kneipp '03. It would have been obvious to one of ordinary skill in the art at the time the invention was made to add additional channels downstream of the restriction barrier of Dorre or Namba to add fluids to the effluent to further process the products after detection or to separate the products according to their type.

7. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to optical tweezers, detection systems and restriction barriers such as filters in microfluidic systems.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571) 272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Arlen Soderquist
Primary Examiner
Art Unit 1797